

The warfarin–cimetidine interaction: stereochemical considerations

The potentiation of the anticoagulant response produced by warfarin upon coadministration with cimetidine is well documented with the proposed mechanism being decreased elimination of warfarin through inhibition by cimetidine of the hepatic cytochrome-P450 drug oxidising system (Breckenridge *et al.*, 1979; Hertz *et al.*, 1979; O'Reilly, 1984).

Clinically, warfarin is administered as a racemic mixture. The enantiomers differ with (S)-warfarin being approximately five times more potent an anticoagulant (Eble *et al.*, 1966) and generally eliminated more rapidly than the (R) enantiomer. Yet, conclusions regarding the cimetidine-warfarin interaction have used non-stereoselective assays for warfarin. We now report stereochemical aspects of the warfarin-cimetidine interaction, using a stereospecific assay.

Two separate studies, approved by an ethics committee, were undertaken in healthy male volunteers, who gave their written consent. In group 1, eight subjects received a single 25 mg oral dose (5×5 mg tablets) of warfarin on day 4 of a 9 day dosage regimen of either placebo or a single 800 mg daily dose of cimetidine, the currently recommended regimen for cimetidine. In group 2, five subjects received a 10 mg oral dose (2×5 mg tablets) of warfarin alone or on day 4 of a 8 day dosage regimen of cimetidine administered as 200 mg three times daily and 400 mg at bedtime, a commonly used regimen of cimetidine. Following the 10 day blood sampling schedule associated with each treatment, a 4 day wash-out period was allowed before administration of the alternate regimen.

The concentration of the warfarin enantiomers in plasma was determined by h.p.l.c. (Banfield & Rowland, 1984), and the pharmacokinetics of each enantiomer were calculated by standard methods (Gibaldi & Perrier, 1982), assuming a one compartment model. The degree of anticoagulation was assessed by both prothrombin time and Factor VII clotting activity. Differences of parameters between control and cimetidine treatment were assessed using a *t*-test, with $P < 0.05$ being considered significant.

The results of the investigation are outlined in Table 1. The 10 mg warfarin dose failed to produce any change in either prothrombin time

or Factor VII activity. Pronounced anticoagulation was seen with the 25 mg dose and the degree of response was quantitated by the areas under the prothrombin time (AUC_p) and Factor VII clotting activity (AUC_{VII}) time curves. Although the general trend was for cimetidine to potentiate the pharmacological response to warfarin, as seen by the slight increase in the mean values of both AUC_p and AUC_{VII} , the changes were not found to be statistically significant. However, the mean result masks the considerable variability in response with five out of the eight volunteers showing a clear increase in response with cimetidine coadministration. Such variability in the effect of cimetidine agrees with earlier findings (Hertz *et al.*, 1979; O'Reilly, 1984). In both studies cimetidine had no effect on the pharmacokinetics of (S)-warfarin, but did affect the pharmacokinetics of the (R)-enantiomer. The elimination half-life ($t_{1/2}$) of (R)-warfarin was increased substantially by concurrent cimetidine treatment. As there was no change in the volume of distribution (V), the prolongation in the half-life is caused by a decrease in the clearance (CL) of this enantiomer. This calculation is based on the assumption that warfarin was completely absorbed (bioavailability, $F = 1$), which is supported by the estimated volume of distribution (12–15 l) being the same as that reported following intravenous warfarin administration (Nagashima & Levy, 1969). This observation appears to be the first example of an interaction with warfarin involving a selective effect on the less potent (R)-warfarin. Other interactions with, for example, phenylbutazone (Banfield *et al.*, 1983) and sulphinpyrazone (Toon *et al.*, 1985) primarily involve inhibition of (S)-warfarin elimination.

The metabolic fate of the warfarin enantiomers differ markedly; (S)-warfarin is metabolised primarily by oxidation ($\approx 90\%$) whilst the (R) enantiomer is metabolised by both oxidation ($\approx 60\%$) and reduction ($\approx 40\%$) (Banfield *et al.*, 1983; Toon *et al.*, 1985). Cimetidine is often quoted as being a classical inhibitor of cytochrome P-450 (Bauman *et al.*, 1982), the enzyme system responsible for the majority of drug oxidations. Consequently, one would have anticipated that, if anything, cimetidine would affect the enantiomer metabolised primarily by

Table 1 Pharmacokinetic parameters (mean \pm s.d.) defining the disposition of the warfarin enantiomers in the absence and during chronic cimetidine administration

Group 1 (n = 8)				
Parameter		Control	Cimetidine	
V/F (l)	(R)	13.25 ± 2.65	14.00 ± 2.42	NS
	(S)	13.94 ± 3.65	13.67 ± 2.55	NS
$t_{1/2}$ (h)	(R)	39.58 ± 6.81	53.36 ± 12.50	$P < 0.01$
	(S)	29.51 ± 5.95	31.30 ± 5.74	NS
AUC (mg l ⁻¹ h)	(R)	55.22 ± 10.97	69.67 ± 16.27	$P < 0.01$
	(S)	40.27 ± 12.41	41.63 ± 10.12	NS
CL/F (ml h ⁻¹)	(R)	233.8 ± 42.6	187.3 ± 38.6	$P < 0.001$
	(S)	332.6 ± 85.1	314.8 ± 69.3	NS
AUC _p (s h)		2264.6 ± 95.8	2327.1 ± 198.7	NS
AUC _{vII} (s h)		2272.1 ± 124.0	2331.5 ± 212.4	NS
Group 2 (n = 5)				
V/F (l)	(R)	11.75 ± 3.0	13.10 ± 3.3	NS
	(S)	15.70 ± 5.6	15.55 ± 5.9	NS
$t_{1/2}$ (h)	(R)	40.2 ± 11.1	60.1 ± 11.0	$P < 0.01$
	(S)	39.6 ± 9.1	40.5 ± 8.7	NS
CL/F (ml h ⁻¹)	(R)	210.0 ± 6.5	160.0 ± 6.5	$P < 0.005$
	(S)	260.0 ± 42.0	280.0 ± 11.5	NS

oxidation, namely (S)-warfarin (O'Reilly, 1984). Yet, it is the elimination of (R)-warfarin, not the (S)-enantiomer, that is inhibited. Whether cimetidine stereoselectively inhibits the oxidation of (R)-warfarin, via its primary oxidative metabolic pathway forming 6-hydroxy-(R)-warfarin, or selectively inhibits reduction of (R)-warfarin, to form (RS)-warfarin alcohol, remains to be determined. Nonetheless, the present findings stress the importance of stereochemistry when considering interactions of drugs with warfarin.

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